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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/869,696	10/31/2001	Donald Davies	2190/49927	8654

23911 7590 08/23/2005

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 08/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/869,696	DAVIES, DONALD	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-54,56,57,59-61,63,65-76,78,79,81 and 84-87* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-54,56,57,59-61,63,65-76,78,79,81 and 84-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 5/24/05. Claims 1-40, 55, 58, 62, 64, 77, 80, 82 and 83 have been canceled. Claims 41, 46, 47, 50, 52, 59, 61, 67-69, 72 and 74 have been amended. Claims 41-54, 56, 57, 59-61, 63, 65-76, 78, 79, 81 and 84-87 are pending.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn. There are no new grounds of rejection herein and therefore, this action is final.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101, which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 41, 60 and 85 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 8 of copending Application

No. 10/258,760. **This rejection is maintained for reasons of record in the office action mailed 2/24/05 and restated below.**

Although the conflicting claims are not identical, they are not patentably distinct from each other because the cited claims of the instant invention are generic to all that is recited in claim 8 of copending Application No. 10/258,760 because both sets of claims recite methods of administration to a mammal of a polypeptide with p450 activity such as CYP1A2, CYP2E1 and CYP3A4. That is, the cited claim of 10/258,760 anticipates and falls entirely within the scope of the rejected claims of the instant application. Specifically, the instant claims recite that the target is cell killing of cancer cells, while application 10/258,760 recites that the target is a non-cancer cell. Absent evidence to the contrary administration of a vector encoding a p450 enzyme accompanied by acetaminophen leads to non-discriminatory killing and therefore, non-cancer and cancer cells would be expected to be subject to cell killing.

Additionally, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding a patent from 10/258,760, then two different assignees would hold a patent to the claimed invention of 10/258,760, and thus improperly there would be possible harassment by multiple assignees.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Argument

Applicants' statement that the provisional double patenting rejection need not be responded to at this time on page 5 of the amendment filed 5/24/05 is acknowledged. However, until the recited claims are patented or a terminal disclaimer is filed, the claims remain rejected.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41-54, 56, 57, 59-61, 63, 65-76, 78, 79, 81 and 84-87 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating cancer in a non-human comprising administration to a mammal of acetaminophen and a vector comprising a polynucleotide encoding CYP1A2, CYP2E1 or Cyp3A4, does not reasonably provide enablement for treating cancer in a human. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims. **This rejection is maintained for reasons of record in the office action mailed 5/24/05 and restated below.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat.

App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. The invention recites a composition comprised of acetaminophen and a vector encoding CYP1A2, CYP2E1 or Cyp3A4 and methods of using these compositions to treat cancer. The invention utilizes disciplines of molecular biology, virology and clinical technology.

2) **Scope of the invention**. CYP1A2, CYP2E1 and CYP3A4 function to convert acetaminophen into a metabolite called N-acetylbenzoquinoneimine (NABQI). In normal liver cells higher levels of glutathionine reacts with NABQI to convert it to a non-toxic substance. Cancer cells do not have the glutathione levels to counter NABQI and thus conversion of acetaminophen to NABQI in the cancer cells leads to cytotoxicity. Thus several dependent claims recite methods of decreasing glutathionine in the cancer cells and to directing the vectors encoding CYP1A2, CYP2E1 and CYP3A4 specifically to cancer cells. In these cases, rodent or another non-human form of CYP1A2, CYP2E1 and CYP3A4 can be introduced into the cancer cells with furaphylline which inhibits human CYP1A2. In this instance, normal cells are protected due to the inhibition of NABQI generation.

The method of the instant invention is directed toward gene therapy in mammals and humans using gene delivery protocols such as viral vector delivery. The only disclosed utility for practicing the claimed methods is for gene therapy. These steps of gene therapy using a viral vector in humans exacerbate an already complex method.

3) **Number of working examples and guidance**. The disclosure teaches the administration of CYP1A2 in the presence of acetaminophen in *in vitro* cell systems. The instant

examples are directed to methods of establishing stable and transient cell lines expressing p450. Experiments with transfected COS and H1A2 MZ cell lines demonstrate that *in vitro* acetaminophen in the presence of CYP1A2, leads to cell death. Variable bystander effects were identified in several cell lines incubated concurrently with H1A2 MZ cells, which stably express CYP1A2.

The instant specification fails to demonstrate any examples or specific guidance for introduction of the composition comprising a vector encoding a polypeptide having p450 activity and acetaminophen into a mammalian subject. While guidance for administration of polynucleotides to a subject are provided, the guidance is broad and general i.e. administration includes but is not limited to intravenous, intramuscular, intraperitoneal injection or direct injection into the tumour tissue (page 10, line 21-24). There are no disclosures for *in vivo* concentration of vector or acetaminophen, no dose schedules and no determination of subjects for which the method would be directed.

Applicants have provided a Declaration, filed 1/24/05, by Dr. Davies. Dr. Davies presents data that show that using the methods of the instant invention in a variety of *in vitro* tumor cell lines, increased sensitivity to cell killing following administration of Ad vectors expressing human or mouse CYP1A2 and acetaminophen. Applicants demonstrate experimentally that the levels of glutathionine can be modulated using buthionine sulphoximine and cell killing is improved under these circumstances. Furthermore, applicants provide date that furaphylline leads to selective inhibition of hCYP1A2 over mCYP1A2. Finally, applicants provide an animal model HepG2 xenograft Balb/C mice to which is administered adenoviral vector expressing mouse or human CYP1A2. The mice were injected with the vectors i.t.

followed by i.p. administration of acetaminophen or paracetamol. 505 of the tumors regressed or remained the same size.

4) **State of Art**. The art of gene therapy for the treatment of cancer is a high art. Enormous efforts have been directed toward the development of gene therapy vectors and for cancer treatments. Each goal alone is complex and requires great skill in the art.

5) **Unpredictability of the art**. The art of the instant invention is unpredictable for treatment of cancer in humans for the following reasons. 1) The method of delivery of polynucleotides is highly unpredictable to date. Gene delivery has been a persistent problem for gene therapy protocols and the route of delivery itself presents an obstacle to be overcome for the application of the vector therapeutically. Verma et al (Verma et al. Nature, September 1997) teach, "The Achilles heel of gene therapy is gene delivery... the problem has been an inability to deliver genes efficiently and to obtain sustained expression". To date, no single mode of gene transfer has provided a viable option for successful gene therapy protocols.

Applicants propose and demonstrate use of viral vectors for delivery. The art of viral vector use for gene delivery is highly unpredictable in the art. Tropism of the viral vectors does not result in targeted administration of the composition. Meng and Deiry (Gene Therapy of Cancer, 1999, page 6, column teach that means of delivery other than intratumoral injection compound the obstacles associated with adenoviral use. "Tropism for organs such as liver, for example by adenovirus, can be a disadvantage if delivery is intended elsewhere or may be advantageous of the liver is the target. Even with regional intravascular administration, the virus must traverse the endothelial wall and travel against pressures within an expanding tumor mass". "While reasonably accurate gene delivery can be achieved by direct inoculation of plasmids or

recombinant viruses using a needle positioned in a tumour deposit. This strategy achieves a relatively low efficiency of gene delivery, which is confined to tumour cells immediately adjacent to the needle track. Plasmids or viral particles delivered in this way do not permeate freely through the interstitial fluid bathing the tumour." (Russell, p 1165, column 2). Therefore, it is unpredictable that administration of the composition will lead to targeted delivery to the appropriate sites.

2) The level of infection necessary to achieve therapeutic affects of the heterologous gene without toxicity to normal cells that results from leaky expression of the viral genes required for replication is unknown. Given the unpredictability of directed delivery, bystander killing would result in surrounding cellular death. Finally, as noted by Marshall, (Marshall et al., Science January 17, 2003) one of the main issues in using retroviral vectors for gene therapy is determining how to use the vector in vivo without causing leukemia or other cancers in the patients being treated. This is not merely a safety issue for FDA concern but is a fundamental issue underlying how the skilled artisan can make and **use** the claimed invention for the recited treatments. No viral vector has proven adequate sources of gene delivery vehicles to date.

3) Applicants have provided evidence *in vitro* and *in vivo* in a Declaration by Donald Davies filed 1/24/05 that the methods of the instant invention lead to enhanced cell killing. However, the ability to predict the potential for success in humans based upon these results is highly unpredictable. While *in vitro* cell culture and *in vivo* animal models have been provided as evidence of success of treatment, these results rarely correlate well with *in vivo* clinical trial results in patients and have not translated into successful human therapies. It is not clear that reliance on experimental models accurately reflects the relative superiority or efficacy of the

claimed therapeutic strategy and applicants present no disclosed or art recognized nexus between the *in vitro* transfection systems and the human disease state. A study by National Cancer Institute demonstrated that using xenograft models do not handle drugs in the same way that the human body does and cell culture provides no information about whether a drug will make it to target sites or not (see e.g. Gura, Science, page 1041, col 1). Ultimately the xenograft model system identifies agents that are effective in treating mice but not humans (see e.g. page 1041, col 2, last paragraph).

6) **Summary**. The invention recites a complex series of methods for the treatment of cancer using a vector CYP1A2, CYP2E1 and CYP3A4 and acetaminophen. The unpredictability of using the claimed invention in gene therapy is accentuated due to the lack of methods or processes disclosed in the instant specification exacerbate a highly unpredictable art.

In view of predictability of the art to which the invention pertains and the lack of established clinical protocols and the inability to predict successful administration of the compositions: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Response to Argument-35 USC 112, first paragraph

Applicants traverse the claim rejections under 35 U.S.C. 112, first paragraph for lack of enablement on pages 11-16 of the amendment filed 1/24/05. Applicants' arguments are the following. Applicants argue that improper legal standard has been applied in making the rejection of the instant claims under 35 USC 112, first paragraph. To this end, applicants argue that multiple patents have been issued with method claims that lack *in vivo* and clinical data. And that arbitrarily distinguishing between human and non-treatment methods is scientifically unsound and no longer pertinent because Dr. Davies is said to demonstrate positive *in vivo* data that the theoretical difficulties in gene delivery are not applicable to the method of the instantly claimed invention. Furthermore, applicants argue that it has been widely accepted that an animal *in vivo* model generally correlates with human treatment methods. Enablement does not depend upon a therapeutic method being ready for clinical data, which applicants support by citing MPEP 2164.02. Applicants argue that in not finding the Declaration of Dr. Davies non-persuasive applicants have ignored his qualifications and reasoned statements. It is applicants' stance that absent evidence to the contrary, the examiner should accept persuasive arguments. References cited by the examiner in support of their position are said not to actually not support the office action (more fully discussed below). Applicants provide three references, which are said to demonstrate that gene-directed enzyme-prodrug therapy is "reasonably predictive of having the asserted therapeutic utility".

Applicants' arguments filed 5/24/05 have been fully considered but they are not persuasive. As to the patentability of the instant case in light of similar claims in published patents that possess similar disclosures, rejections based upon this argument have been addressed

in *in re* Giolito and Hoffman. "It is immaterial whether similar claims have been allowed to others" (see *in re* Giolito and Hoffman 188 USPQ 645). Rather, each application is reviewed on its own merits.

"The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." In the instant case, the disclosure is limited to *in vitro* methods of cell ablation. Applicants have demonstrated the operability of the claimed invention for introduction of adenoviral vectors i.p. into HepG2 xenograft Balb/C mice for partial regression or stasis of tumors in post-filing experiments. While these experiments have relied on methods not disclosed in the specification, they have demonstrated that in an *in vivo* model, the instant method has potential in meeting the methods of the recited claims, which are drawn to *in vivo* treatment of cancer in humans. First of all, the data from the *in vivo* mice models does not demonstrate that cancer has been treated. As well, applicants recite a large genus of cancers that are to be treated by the instant methods including breast, pancreatic, ovarian, cervical, lung, hepatic etc. It is unclear how to extrapolate the results from the Balb mice to the actual methods that are recited. Secondly, the specification by providing no methods does not advance the *in vivo* data. Therefore, one must look to the art to determine the state of gene therapy in the art at the time of filing. In so doing, the relevant articles have demonstrated that at the time of filing a) gene delivery to subjects was hindered by lack of sustained and efficient expression (Verma) b) Efficiency of delivery and targeted delivery were highly unpredictable (Meng and el-Deiry) c) The most efficient method to date has been identified as direct inoculation which in fact has been found not to permeate through the interstitial fluid (Russell) d) toxicity of viral gene delivery has

been detected (Marshall) e) mouse xenograft models for cancer treatment do not correlate with treatments in humans (Gura).

Applicants have argued that these references do not teach against the instant invention. Applicants state that at least two forms of gene therapy present far fewer challenges such as *ex vivo* and direct intratumoral injection. Applicants also argue that Meng and Deiry teach that the most direct route of delivery is intratumoral. In response, it is noted that when gene therapy emerged as a means to treat disease, it had much promise. Multiple approaches were considered to be with promise to mediate desired responses. However, the actual use of delivering genes to cells such as with adenovirus has not materialized. In fact, Russell et al teach that intratumoral injection is highly faulty and actually inefficient (Russell et al page 1165, col 2, paragraph 4-5).

Furthermore, applicants argue that Verma and Somia teach that adenoviral vectors are useful for expression during short periods of time and speak to the promise associated with delivery of large numbers of vectors containing genes encoding enzymes that activate to kill cancer cells. Applicants point to Russell et al as teaching that use of replicating gene-transfer vectors for human therapy theoretically have potential which is enhanced by bystander killing of uninfected tumor cells using vector encoded enzyme. Again, while the potential for actual efficient targeted gene delivery is hoped for, the means to do so have not been demonstrated.

Applicants also argue that the citation of Marshall et al is not related to enablement but with regulatory approval. Applicants also argue that their invention is exemplified using adenoviral vectors. The enablement of the instant invention has been assessed in light of the specification and the prior art available at the time of filing. "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the

specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). In the instant case, there are multiple inoperative embodiments when considering the use of the instant invention in humans; 1) means of safely and efficiently introducing the DNA encoding CYP1A2, CYP2E1 and CYP3A4 into the cell 2) a lack of means to target vector efficiently to point of treatment 3) a means to avoid toxicity of normal cells 4) lack of correlation between the provided *in vitro/in vivo* models and the human subjects with cancer. In light of the art at the time of filing, the instant invention would require undue experimentation to perform the invention in humans. However, clinical studies have not been requested nor are required to validate the instant invention.

Finally, applicants argue that while not 100% predictive, animal models function to screen and are among the best models available. However to this end, the MPEP teaches

(2164.02) "In this regard, the issue of "correlation" is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition. In re Brana, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that in vitro data did not support in vivo applications)."

Use of xenograft mice models has not been demonstrated to be an art recognized model for cancer treatment in humans as demonstrated by Gura et al. However, in considering whether the provided mouse reasonably correlates with cancer it must be considered that applicants have recited multiple targets ranging from renal to mesothelial cancer. It cannot be reasonably

concluded that the xenograft model with hepatocellular carcinoma functions as a correlative model for human cancer.

In the instant case, Applicants argue that they have provided three references to counter these claims for lack of enablement. The first by Sausville is simply a review of the results of Palmer et al, which are provided in the second and third article provided by applicants. The method of Palmer et al is similar to the instant method in that it is directed toward Virus or gene directed enzyme prodrug therapy. Palmer et al, J Clinical Oncology, presents data from intratumoral inoculation of vector encoding enzyme (nitroreductase) into patients with primary and secondary liver cancer. The virus is tolerated and expression of nitroreductase detected. With regard to the post-filing references, any differences between their teachings and the instant specification must be considered as inventive experimentation considering the underdeveloped state and unpredictability of the art at the time of applicants' invention (see above). For example, Palmer et al more recently have demonstrated that use of adenovirus vectors in VDEPT promotes cell survival not death. The survival is due to activation of NF-κB activation and has a negative effect on the strategy of VDEPT (see e.g. abstract). Hence, Palmer et al have included a therapy directed against NF-κB for successful therapy. However, the instant specification provides little guidance for the recited methods. As well, the art teaches that at the time of filing, the art was underdeveloped and highly unpredictable. Therefore, given the lack of guidance in the specification and the prior art, it is concluded that a person of skill in the art would have had to conduct undue unpredictable experimentation in order to practice the claimed invention.

Conclusion

No claims are allowed.

1. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, David Nguyen, PhD can be reached on (571)-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1633

August 19, 2005

JAMES KETTER
PRIMARY EXAMINER